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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/325,095	06/03/99	HILES I	LUD5246.4JEL

HM12/1012

FELFE & LYNCH
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NEW YORK NY 10022

EXAMINER
HINES,J

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/12/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/325,095	Hiles et al.
Examiner	**Group Art Unit**
Ja-Na Hines	1641

☒ Responsive to communication(s) filed on *Jun 3, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-36* is/are pending in the application.

Of the above, claim(s) *1-26* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *27-36* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Drawings

1. The drawings are objected to because of the reasons set forth in the attached PTOL-948. Correction is required.

Specification

2. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

3. Claim 35 is objected to because of the following informalities: The word hybridizes is spelled as "hypridizes" in line 4. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. Claim 36 recites the term "differences" there-between. This term is vague and indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of differences, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how to define what levels of differences need to be achieved when comparing the contacted substances activity. It is unclear how to define what levels of differences need to be achieved when comparing the activity of the PI3 kinase agonist or antagonist.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 27-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skolnik et al., in view of Carpenter et al. Skolnik et al., teaches the cloning of PI3 kinase and a novel method for expression and cloning of target proteins. One gene (GRB-1) has been fully sequenced and found to be expressed in various tissues and cell lines and has a molecular mass of 85kD (abstract). The GRB-1 encodes the human counterpart of PI3 kinase -associated protein p85 (abstract). The tyrosine phosphorylated carboxy-terminal tail of EGFR (epidermal growth

factor receptor) was used as a probes to screen expression libraries from several different human tissues (page 84 para. 3). To determine the detection of binding of EGFR to an SH2-containing protein immobilized on nitrocellulose filters, the EGFR domain could bind specifically to an SH2-containing protein immobilized on nitrocellulose and this encouraged the authors to supply the screening of the λgt11 expression libraries which was constructed from mRNA isolated from human brain stem (see Figure 1, page 84 para. 2 and experimental procedures). In one experiment, the human brain stem λgt11 library was screen (page 84 para. 2). A single clone, clone ki4 was isolated using a thermal cycler, Taq1 polymerase and oligonucleotide complementary to the EcoR1 flanking regions (see experimental procedures) and found to express GRB-1 and was purified using the ^{32}P labeled carboxy-terminal domain of the EGFR (see Figure 2 and page 84 para. 3). To analyze clone ki4, cDNA was sequenced, see Figure 3. A northern analysis was performed, using Poly(A)$^+$ RNA followed by steps of hybridization with the blot (see experimental procedures) to assess the expression of mRNA corresponding to the newly isolated cDNA wherein the Northern hybridization analyzed monkey tissue using human DNA probes corresponding to the clone ki4 (page 86 para. 3). The blot was hybridized with a ^{32}P labeled nick-translated DNA probe corresponding to the insert from the clone ki4 (Figure 5). The highest levels of expression were found in the brain, with heart, spleen, liver and thymus displaying decreasing levels of expression (page 86 para. 2 and Figure 5). GRB-1 exhibits 96% sequence identity to the murine and bovine p85 forms (page 88 para. 5). The PI3 kinase activity is found associated with the 110 kD tyrosine phosphorylated protein which may the catalytic

subunit of the PI3 kinase (page 88 para. 6). The GRB-2 has been partially sequenced and contains unique src homology (SH) 2 and SH3 domains and the presence of SH2 domains in GRB1 and 2 further reinforce the importance of this domain in mediating the interaction of these proteins, since these proteins are capable of interacting the tyrosine kinase receptors (page 88 para. 5-6). This method overcomes the laborious and costly task of purifying target proteins and provides a method for identifying rare target molecules whose association with activated receptors could not be previously detected due to limited ability of conventional techniques to identify such proteins (page 87 para. 2). The method also allows for the identification of related proteins that are similar in their capacity to bind to activated receptors with tyrosine kinase activity but are only weakly homologous at the DNA level (page 87 para. 2). This is important since conventional screening methods to identify genes such as low stringency screening would be unsuccessful in cloning GRB-1 and GRB-2 because of their lack of similarity at the DNA level (page 87 para. 2), and because one of the most urgent problems in growth control and oncogenesis is the identification of target protein for tyrosine kinases (page 87 para 2). However, Skolnik et al., does not teach the use of the 110kD protein determined by SDS-PAGE.

Carpenter et al., teaches the purification and characterization of phosphoinositde 3-kinase (PI3 kinase) from rat liver. Polyphosphoinositides and their metabolites are essential for intracellular signaling in response to hormones and growth receptors (page 19704). There is a strong correlation between PI3 kinase and cell growth (page 19705). When PI3 was analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis which contained both a 85 kD and a

110 kD protein (abstract). The two protein co-migrated on two-dimensional Western blots, where ^{32}P labeled antigen specifically blots to the p85 protein (abstract). PI kinase activity correlated with the amount of protein found in the upper and lower band of the 110kD bands (page 19705). The two 110kD proteins seems to be very closely related however not identical which suggest the upper and lower bands are products of different genes (page 19707).

With respect to claims 32 and 33, DNA/RNA hybridization consist of allowing single stranded DNA or RNA to reassociate whereas any mismatch is presumably due to evolutionary divergence and will reduce bonding strength between the molecules. However, since no stringency conditions or any other conditions were defined, the use of the PI3 kinase polypeptide of Skolnik et al., in view of Carpenter et al., could hybridize to any of the sequences disclosed in claims 32 and 33.

Therefore, it would have been obvious at the time of applicants invention to have used the 110kD protein as taught by Carpenter et al., in the method of determining gene expression as taught by Skolnik et al., because Carpenter et al., teaches that the 110 kD protein was isolated by SDS-PAGE, is correlated to the PI3 kinase activity, strongly related to cell growth activity, its gene products can be found of different genes and is crucial in intracellular signals which respond to a number of hormones and growth factors.

Prior Art

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Escobedo et al., (Mol. and Cell.) teaches a PI3 kinase that binds to PDGFR and the association of a 110kD proteins. Escobedo et al., (Cell) teaches the p85 protein and a 110 kD protein which are subunits of the PI3 kinase. Otsu et al., teaches bovine PI3 kinase which contain two major proteins, a 85 kD and a 110kD protein.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines

September 27, 1999

James C. Housel

JAMES C. HOUSEL 10/12/99

SUPERVISORY PATENT EXAMINER